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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,936	01/14/2004	Douglas D. Burkett	344-P-32-USA	6529

7590 02/23/2007

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,936	BURKETT, DOUGLAS D.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-12-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/2007 has been entered.

Claims 2-5 have been added. Claims 1-5 are pending and are addressed in this office action.

Previous Rejection

2. The objection to the specification is withdrawn in view of Applicant's amendment. The new matter rejection under 35 USC 112 first paragraph is withdrawn in view of Applicant's arguments and support in the prior art for the use of the term in conjunction with oral and head and neck cancers. The prior art rejection under 35 USC 103(a) is maintained and discussed below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Once again, Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mashberg et al. (A Cancer Journal for Clinicians, Vol. 45, No. 6, pages 328-351, Nov-Dec 1995) in view of Rosin et al. (Clinical Cancer Research, Vol. 6, pages 3557-362, Feb 2000). Regarding claim 1, Mashberg et al teach a prognostic method for early prediction of eventual development of epithelial invasive cancer (oropharynegeal squamous cancers), said method comprising: (a) applying to tissue a staining dye (toluidine blue) that is selectively retained by mitochondria of neoplastic and preneoplatic cells; (b) identifying clonal patches of said tissue by visually examining said tissue for stained tissue sites (page 345, section entitle "Vital Staining", col. 1, beginning at the second full paragraph to page 347, column 1, lines 1-3); (c) resecting tissue in the locus of said patches for subsequent histopathological analysis (page 347, beginning at col. 1, first full paragraph to page 349, column 1, lines 1-28). Mashberg et al teach that the staining dye is useful because it clinically stains neoplastic and preneoplastic cells (malignant and premalignant cells), but not normal mucosa (page 345, lines 28-29 and serves as a guide to biopsy by localizing tumor cells within the area of erythroplasia (page, 346, 13th through 15th lines from bottom of column 2).

The method of Mashberg et al differs from the instant invention in that Mashberg et al do not expressly teach wherein DNA is extracted from the resected tissue and examined for allelic losses or mutation of tumor suppressor genes.

Rosin et al teach method for the analysis of a biopsy tissue sample to identify genetic changes critical to the progression and non-progression of premalignant lesions into epithelial invasive cancer (oral epithelial dysplasia). Rosin identifies the problem

with limiting diagnosis of a cancerous or precancerous condition based on biopsy and pathohistological techniques as taught by Mashberg (see page 1, col. 2, "Introduction") and provides motivation for solving the problem by further performing microsatellite analysis to determine loss of heterozygosity at critical loci. Rosin et al teach wherein the method comprises obtaining paraffin-embedded biopsy tissue samples confirmed by histological diagnosis and at least two pathologists as hyperplasia or mild or moderate dysplasia; microdissecting tissue in the locus of areas identified as hyperplasia, dysplasia, or tumor; extracting DNA from the dissected tissue and determining by polymerase chain-based microsatellite analysis whether the dissected tissue exhibits allelic losses (Abstract and page 358, col. 1, beginning at the second full paragraph (section entitle "sample collection) to column 2, sections entitled "Tissue Microdissection and DNA Extraction" and "LOH analysis"). Rosin et al teach that this method is a more sensitive technique for studying clonal changes in tumors and premalignant lesions. Rosin et al further teach that the advantage of this procedure is that is requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes. Rosin et al states that hence, information critical to genetic events can be obtained even before the identification of the actual suppressor gene (page 357, column 2, third full paragraph).

Therefore in view of foregoing, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have combined the polymerase chain-based microsatellite analysis method of Rosin et al with the staining diagnosis method of Mashberg et al. as a prognostic method for the early prediction of eventual

development of invasive cancer. One of ordinary skill in the art would have been motivated to do so for the advantages taught by Rosin et al that the polymerase chain-based microsatellite analysis method is a more sensitive technique for studying clonal changes in tumors and premalignant lesions in that the method requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes (page 357, column 2, third full paragraph).

Applicant's traversal

5. Applicant traverses the rejection on the following ground: Applicant summarizes the Examiner's rejection and state that there is no teaching or suggestion or motivation to combine or modify the teachings of Mashberg and Rosin to produce the claimed invention. Applicant states that the claimed invention is directed to providing a prognostic method for the early prediction of eventual development of invasive epithelial cancer on epithelial tissue. Applicant states that in contrast Mashberg addresses the diagnosis of oral and oropharyngeal cancers. Applicant states that the difference is that Applicant's claimed invention provides a method for predicting whether epithelial cancer is likely to develop in the further and Mashberg discloses method for diagnosing a cancerous condition that is already inexistence in its early stages. Applicant states that in other words, Applicant's claimed invention provides a prognosis whereas Mashberg provides a diagnosis. Applicant states that Applicant's claimed invention is based on the surprising an unexpected discovery that toluidine blue stains not only cancerous tissue, but also precancerous tissue, and further that such precancerous tissue may

provide the earliest indications of genetic alterations which are precursors to the development of invasive cancer.

Applicant states that in contrast, Mashberg does not disclose, teach or suggest that toulinde blue may be use to locate precancerous or clonal tissue. Applicant states that instead Mashberg would interpret such a result as a "false positive" as Mashberg teaches that "toluidine blue" clinically stains malignant lesion, but not normal mucosa. Applicant asserts that they have discovered that toluidine blue may be used to identify tissues that may be subjected to further genetic analysis. Applicant state that this molecular analysis definitively shows that approximately 80% of the lesion identified by the Mashberg-type protocol are clonal (specification page 17). Applicant states that the "preneoplastic changes identified by the toluidine blue dye in this patient population are clonal and are therefore in the progression pathway to cancer (specification page 18-19). Applicant states that there would be no motivation to combine Mashberg with Rosin, as the disclosure in Mashberg is limited to providing a diagnosis of oral and oropharyngeal cancers and does not teach the prognostic method for the future development of epithelial cancer that is described and claimed by Applicant. Applicant states that therefore, because there is no teaching, suggestion or motivation to combine Mashberg and Rosin, and because of the demonstrated surprising and unexpected results from the claimed 103 should be withdrawn.

Examiner's Response

6. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Examiner respectfully disagrees and maintains that the combination of Mashberg in view of Rosin meet the limitations of the claims. In response to Applicant's arguments that Mashberg et al differs from the instant invention in that it provides a diagnosis of oral and oropharyngeal cancers, the Examiner agrees but reminds Applicant that the rejection is not limited to only the teaching of Mashberg alone, but is based on the combination of Mashberg in view of Rosin. Likewise, Mashberg, like Applicant, performs the same steps of applying a staining dye to epithelial tissue which in this case is toluidine blue. Mashberg, like Applicant, visually examines said tissues for stained tissue sites, thus identifying clonal patches and then resect said tissue sites by performing a biopsy of the suspected tissue(s).

Mashberg only differs from Applicant in that the reference does not teach wherein DNA is extracted from the resected tissue and a prognosis determined by examining allelic loss or mutations of tumor suppressor genes. These limitations are found in the secondary reference of Rosin.

Rosin et al teaches a method for predicting malignant risk for epithelial cancer by examining allelic loss or mutation of tumor suppressor genes in DNA extracted from resected epithelial tissue. Rosin recognizes the limited ability to provide a diagnosis or prognosis for developing invasive epithelial cancer and provides motivation for performing a more sensitive technique as discussed in the rejection. Thus, the Examiner maintains that the combination of Mashberg in view of Rosin meets the limitations of the claims.

In response to Applicant's arguments that Mashberg does not teach locating precancerpus or clonal tissues, the Examiner disagree because Mashberg teaches that:

(a) toludine blue clinically stains malignant lesions, but not normal mucosa;

(b) toluidine blue stains all or part of all malignant lesion;

(c) toluidine blue stains dysplastic lesions; normal intact mucosa does not absorb the stain, but small areas of mechanically retained dye occasionally may be observed;

(d) typical early carcinoma, an area of erythroplasia with or without a white component stains dark blue

(e) Areas of inflammation may also stain blue, but are usually resolved by the time the patient is restained fourteen days later. Mashberg teaches that if the lesions are dark blue after the fourteen-day waiting period, the probability of malignancy is greatly increased (see pages 345-347).

(f) Mashberg further states that the great value of toluidine blue staining lies in its control over false -negatives clinical findings (i.e., it detects lesions too subtle to

be clinically appreciated, and it discloses which innocuous appearing lesions are most deserving of additional work-up (page 347, last paragraph of col. 2).

(g) Likewise, Applicant's specification performs the *same* procedures carried out by Mashberg (see Applicant's specification and Example 1) and supports the use of Mashberg's toluidine dye in detecting cancerous and precancerous lesions (see Applicant's specification at page 4, 9-13). The only differences between the teachings of Mashberg and Applicant is that Applicant performs further molecular analysis techniques which are provided in the secondary reference of Rosin.

In response to Applicant's arguments concerning the teaching at pages 18-19 of the instant specification, it is noted that the instant specification do not recite pages 18 and 19. There are only 17 pages in the instant application. Accordingly, those pages could not be confirmed.

In response to Applicant's arguments that Mashberg is limited to providing a diagnosis not a prognosis, it is again noted that the instant rejections are not limited to only Mashberg, but are based on Mashberg in view of Rosin. Like applicant, Rosin provides the bases for making a prognosis based on further microsatellite analysis to determine allelic loss and provides motivation for wanting to utilize this technique.

Applicant's arguments are not sufficient to overcome the prior art rejection. Accordingly, the rejection is maintained.

New Ground(s) of Rejections

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mashberg et al in view of Rosin as previously applied above. Regarding claim 2, Mashberg et al teach a method comprising applying a dye that is retained by

mitochondria of neoplastic and preneoplastic cells to the epithelial tissues[1] (see pages 345-347).

Mashberg et al do not teach wherein the epithelial tissue that is stained with the dye is subjected to microsatellite analysis to determine loss of heterozygosity.

Rosin et al teach a method for the molecular analysis of a biopsy tissue sample to identify genetic changes critical to the progression and non-progression of premalignant lesions into invasive cancer. Rosin identifies the problem with limiting diagnosis of a cancerous or precancerous condition based on biopsy and pathohistological techniques as taught by Mashberg (see page 1, col. 2, "Introduction") and provides motivation for solving the problem by further performing microsatellite analysis to determine loss of heterozygosity at critical loci. Rosin et al teach wherein the method comprises obtaining paraffin-embedded biopsy tissue samples confirmed by histological diagnosis and at least two pathologists as hyperplasia or mild or moderate dysplasia; microdissecting tissue in the locus of areas identified as hyperplasia, dysplasia, or tumor; extracting DNA from the dissected tissue and determining by polymerase chain-based microsatellite analysis whether the dissected tissue exhibits characteristics associated with cell differentiation or cancer by analyzing markers at different loci that have been previously shown to be frequently lost in certain cancers (Abstract and page 358, col. 1, beginning at the second full paragraph (section entitle "sample collection) to column 2, sections entitled "Tissue Microdissection and DNA Extraction" and "LOH analysis"). Rosin et al teach that this method is a more sensitive

[1] Note* Mashberg utilizes toluidine blue which is the same dye used by Applicant. Accordingly, the dye being retained in the mitochondria of neoplastic and preneoplastic cells is an inherent property of toluidine blue.

technique for studying clonal changes in tumors and premalignant lesions. Rosin et al further teach that the advantage of this procedure is that it requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes. Rosin et al states that hence, information critical to genetic events can be obtained even before the identification of the actual suppressor gene (page 357, column 2, third full paragraph).

page 357, column 2, third full paragraph).

Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have combined the polymerase chain-based microsatellite analysis method of Rosin et al with the staining diagnosis method of Mashberg et al. as a prognostic method for determining the likelihood of cancer in epithelial tissue based on the advantages taught by Rosin et al that the polymerase chain-based microsatellite analysis method is a more sensitive technique for studying clonal changes in cancerous and precancerous lesions and could serve as an initial screening for cancer risk of early premalignancies (see abstract)

It would have been *prima facie* obvious to one of ordinary skill in the art to utilized the polymerase chain-based microsatellite analysis method of Rosin et al in the staining diagnosis method of Mashberg for the obvious benefits taught by Rosin et al that the polymerase chain-based microsatellite analysis method requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes (page 357, column 2, third full paragraph).

Regarding claims 3-5, Rosin et al teach wherein the microsatellite analysis is conducted at any one or a combination of chromosomes 3p and 9p and 17p (see abstract and page 358, col. 1, first full paragraph and section entitled "LOH analysis). Rosin further teaches that LOH of 3p and/or 9p are frequently lost in oral tumors and head and neck tumors and is therefore a prerequisite for progression and may be used as an initial screening for assessing risk of epithelial premalignancies (see discussion as pages 361-362 and Table 3).

Prior Art

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mao et al. (Nature Medicine, vol. 2, no. 6, pages 682-685, June 1996) teach frequent microsatellite alterations at chromosomes 9p and 3p in oral premalignant lesions and their value in cancer risk assessment.

Conclusion

11. No claims are allowed. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

cbw

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